FORMULATION AND EVALUATION OF BILAYER TABLETS OF METFORMIN HYDROCHLORIDE SR AND VILDAGLIPTIN IR

Dissertation

Submitted to

The Tamil Nadu Dr.M.G.R Medical University, Chennai

In Partial fulfillment for the award of the degree of

MASTER OF PHARMACY

In

PHARMACEUTICS

By

REG NO.261210301

DEPARTMENT OF PHARMACEUTICS

ULTRA COLLEGE OF PHARMACY

4/235, COLLEGE ROAD, THASILDAR NAGAR,

MADURAI – 625020.

APRIL - 2014

DECLARATION

I Hereby declare that this thesis work entitled ″ **FORMULATION AND EVALUATION OF BILAYER TABLETS OF METFORMIN HYDROCHLORIDE SR AND VILDAGLIPTIN IR**" Submitted to The Tamil Nadu Dr M.G.R Medical University, Chennai was carried out by me in the Department of Pharmaceutics, Ultra College of Pharmacy ,Madurai Under the Valuable and Efficient Guidance of **Mrs,C.VIJAYA, M.PHARM., Phd**., Dean, Department of pharmaceutics, Ultra College of Pharmacy Madura. During the academic Year March 2013-April 2014 ,I also declare that the matter Embodied in it is a genuine work and the same has not formed the basics for the award of any degree, Diploma, Associateship, fellowship of any other University Or Institution .

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During this period his conduct was found to be good.

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EXAMINERS

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translate their Dreams in to reality all other persons who helped me out either in educational carrier or during the personal life. I want to say the single word which express to all.

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REG. NO: 261210301

DEDICATED
TO
MY
BELOVED PARENTS, KARTHIKA &RITHIKA

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1. INTRODUCTION

1.1 DIABETES[1]

Diabetes is a chronic disease in which body does not make or properly use insulin, a hormone that is needed to convert glucose and other food in to energy. Diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. Patients with high blood sugar will typically experience polyuria (frequent urination), they will become increasingly thirsty (polydipsia) and hungry (polyphagia).

There are three types of diabetes:

1). Type 1 Diabetes[2, 3]

The body does not produce insulin. Some people may refer to this type as insulin-dependent diabetes, juvenile diabetes, or early-onset diabetes. People usually develop type 1 diabetes before their 40th year, often in early adulthood or teenage years. Type 1 diabetes is nowhere near as common as type 2 diabetes. Approximately 10% of all diabetes cases are type 1.

2) Type 2 Diabetes

The body does not produce enough insulin for proper function, or the cells in the body do not react to insulin (insulin resistance).Approximately 90% of all cases of diabetes worldwide are of this type. Some people may be able to control their type 2 diabetes symptoms by losing weight, following a healthy diet, doing plenty of exercise, and monitoring their blood glucose levels. However, type 2 diabetes is typically a progressive disease - it gradually gets worse - and the patient will probably end up have to take insulin, usually in tablet form. Overweight and obese people have a much higher risk of developing type 2 diabetes compared to those with a healthy body weight. People with a lot of visceral fat, also known as central obesity, belly fat, or abdominal obesity, are especially at risk. Being overweight/obese causes the body to release chemicals that can destabilize the body's cardiovascular and metabolic systems. Being

overweight, physically inactive and eating the wrong foods all contribute to our risk of developing type 2 diabetes.

3) Gestational Diabetes

This type affects females during pregnancy. Some women have very high levels of glucose in their blood, and their bodies are unable to produce enough insulin to transport all of the glucose into their cells, resulting in progressively rising levels of glucose. Diagnosis of gestational diabetes is made during pregnancy. The majority of gestational diabetes patients can control their diabetes with exercise and diet. Between 10% to 20% of them will need to take some kind of blood-glucose-controlling medications. Undiagnosed or uncontrolled gestational diabetes can raise the risk of complications during childbirth.

MECHANISM OF ACTION OF INSULIN[4-6]

Insulin initiates the action by binding to a glycol protein receptor on the surface of the cells. Insulin released in to the blood by blood by B cells in the pancreas response to rising levels of glucose. Insulin absorbs glucose from blood for use as fuel, conversion other needed molecule, or for storage. Insulin converts glucose to glycogen for internal storage of liver and muscle cells. Reduced the glucose levels result in both in reduced the level of insulin from B cells and reverse conversion of glycogen to glucose, when glucose level falls. These mechanism of action of insulin regulating the carbohydrate and lipid metabolism are illustrated in Fig 1.

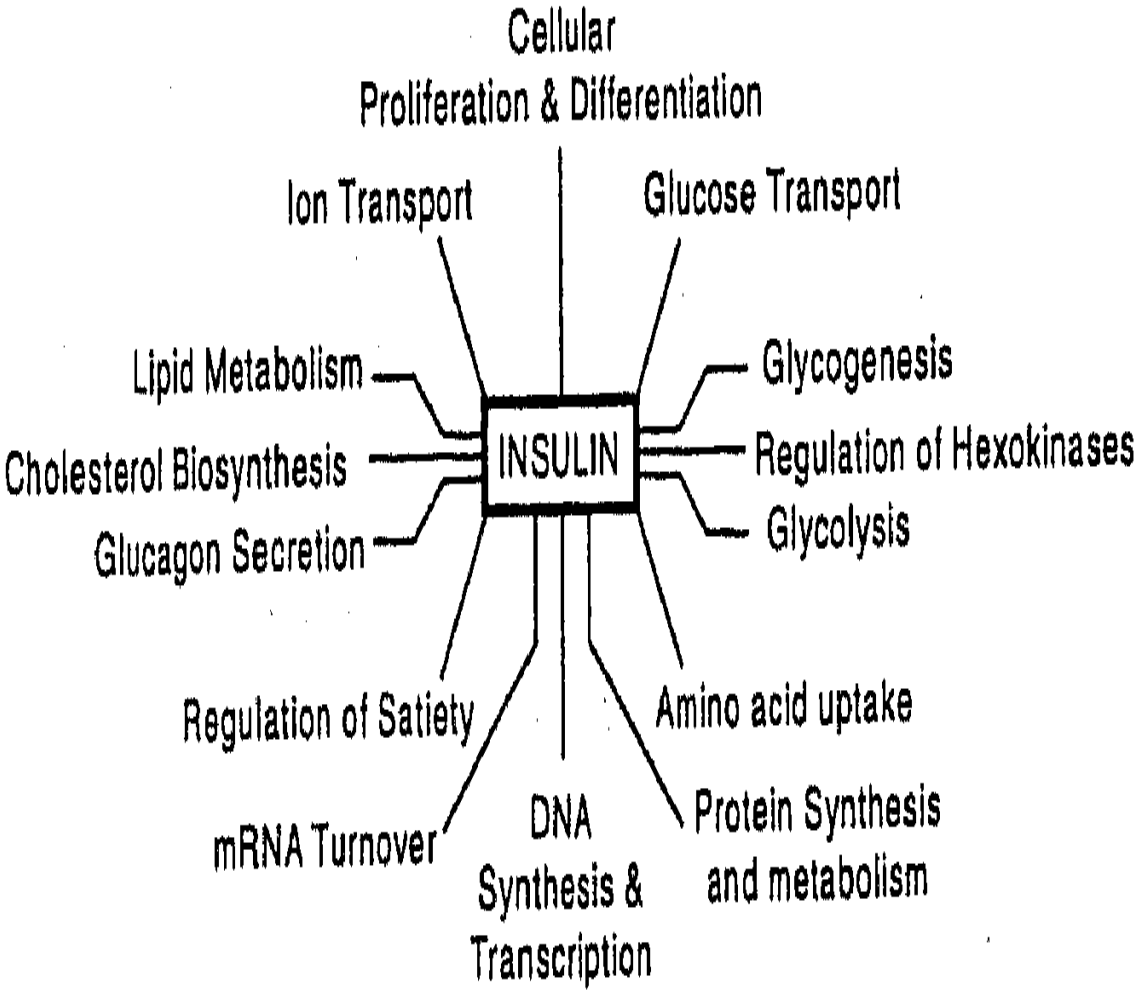

Figure 1. Insulin is involved in the regulation of a wide range of vital metabolic pathways and cellular functions. Its deficiency leads to diabetes and related disorders.

Categories and effects:

Five kinds of oral anti-diabetic drug[7, 8]are used to treat diabetes.

1. **Sulfonyl urea's:** stimulate the pancreas to release insulin.
2. **Meglitinides :** Stimulate the pancreas to release insulin.
3. **Biguanides :** such as Glucophage reduce gluconeogenesis in the liver.
4. **Thiazolidinediones:** such as Actos improve insulin resistance.
5. **Alpha-glycosidase inhibitors:** such as Glucobay decrease glucose absorption from Small intestine.

Oral Anti-diabetic medicines are not recommended for:

1. People with Type 1 Diabetes**.**
2. Women who have had diabetes during pregnancy and breast feeding.
3. Patients who underwent major surgery**.**
4. People who are in massive pressure such as severe injury or infection**.**
5. People who have allergy history of oral anti-diabetic drugs**.**
6. People who have obvious heart failure or liver/renal function impairment

SIDE EFFECTS:

1. **Sulfonylureas:** The primary side effect is hypoglycemia and usually minor skin allergy.
2. **Meglitinides :** The primary side effect is hypoglycemia and minor symptoms are skin **r**ash or itching; gastro-intestinal upset.
3. **Thiazolidinediones:** The medication may cause fluid retention, edema or weight gain.
4. **Biguanides**: The vexing side effect is lactic acidosis, especially using for those who were comorbid with obvious heart failure or liver/renal function impairment. The minor side effects are nausea, diarrhea and gastro-intestinal upset.
5. **Alpha-glycosidase inhibitors**: The main serious side effect is liver function impairment and the less annoying side effects are flatulence or diarrhea.

Cautions:

1. Do not change your dosage or stop using your medicine without discussion with your doctor.

Otherwise, the change of dosage may lead to high blood glucose level.

2. If certain kinds of Sulfonylurea's such as Gliben, Glidiab are taken, the patient should have some food within 30 minutes.
3. Do not titrate dosage of Sulfonylurea's and Meglitinides by yourself, for these two types of the medicines may cause hypoglycemia. The hypoglycemia is more likely to occur if you have your meal irregularly.
4. You might have symptoms, such as weakness, fatigue, dizziness, cold sweating, irritation, palpitation, or hunger when facing hypoglycemia..

1.2 BILAYER TABLETS[9,10]

INTRODUCTION

In the last decade, interest in developing a combination of two or more Active pharmaceutical ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bi-layer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release).

NEED OF BILAYER TABLETS[9]

1. For the administration of fixed dose combinations of different APIs, prolong the drug Product life cycle, buccal / mucoadhesive delivery systems; fabricate novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery.
2. Controlling the delivery rate of either single or two different active pharmaceutical ingredient(s)
3. To modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.
4. To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer (such as, osmotic property).

ADVANTAGES OF THE BILAYER TABLET DOSAGE FORM[9]

1. Bi-layer execution with optional single-layer conversion kit.
2. Cost is lower compared to all other oral dosage form.
3. Greatest chemical and microbial stability over all oral dosage form.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Flexible Concept.
6. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
7. Easy to swallowing with least tendency for hang-up.
8. Suitable for large scale production.

DISADVANTAGES OF BILAYER TABLET DOSAGE FORM[9]

1. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
2. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating.
3. Difficult to swallow in case of children and unconscious patients.
4. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

IDEAL CHARACTERSTICS OF BILAYER TABLETS[9]

1. A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration and contamination.
2. It should have sufficient strength to with stand mechanical shock during its production packaging, shipping and dispensing.
3. It should have the chemical and physical stability to maintain its physical attributes over time.

The bi-layer tablet must be able to release the medicinal agents in a predictable and reproducible manner.

4. It must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

CHALLENGES IN BILAYER TABLETS MANUFACTURIE[10]

Conceptually, bi-layer tablets can be seen as two single-layer tablets compressed into one. In Practice, there are some manufacturing challenges.

Delamination: Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Cross-contamination: When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bi layer tablet. Proper dust collection goes a long way toward preventing cross contamination.

Production yields: To prevent cross contamination, dust collection is required which leads to losses. Thus, bi layer tablets have lower yields than single-layer tablets.

Cost: Bilayer tableting is more expensive than single layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in blazer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation. These factors, if not well controlled/optimized, in one way or another will impact the bi-layer compression per se and the quality attributes of the bi-layer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

Types of bi-layer tablet press:

1. Single sided tablet press.
2. Double sided tablet press.
3. Bi-layer tablet press with displacement monitoring.

1. Single sided press:

The simplest design is a single sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity or forced fed with different power, producing the two individual layers of tablets. When die passes under the feeder, it is first loaded with the first layer powder followed by the second layer powder. Then the entire tablet is compressed in one or two steps.

Limitations of the single sided press:

1. No weight monitoring / control of the individual layers.
2. No distinct visual separation between the two layers.
3. Very short first layer dwell time due to the small compression roller, possibly resulting in poor . deaeration, capping and hardness problems.
4. This may be corrected by reducing the turret rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

2. Double sided tablet press:

In most double sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main compression of the layer. This measured peak compression force is the signal used by the control system to reject out of tolerance and correct the die fill depth when required.

3. Bi layer tablet press with displacement monitoring:

The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the tablet weight but depends on the applied pre compression force.

Advantages:

1. Weight monitoring / control for accurate and independent weight control of the individual layers.
2. Low compression force exerted on the first layer to avoid capping and separation of the two Individual layers.

3. Independence from the machine stiffness.
4. Increased dwell time at pre compression of both first and second layer to provide sufficient hardness at maximum turret speed.
5. Maximum prevention of cross-contamination between the two layers.
6. Clear visual separation between the two layers and maximized yield.

PREPARATION OF BILAYER TABLETS

Bi-layer tablets are prepared with one layer of drug for immediate release with the second layer designed to release drug later, either as a second dose or in an extended release form8. The bi-layer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included. To produce adequate tablet formulation, certain requirements such as sufficient mechanical strength and desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression: it is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation: it is the property of the material in which there is increased mechanical strength due to inter particulate interaction (bonding). The compression force on layer 1 was found to be major factor influencing tablet delamination. The scheme of preparation of bilayered tablets is given in Fig no.2.

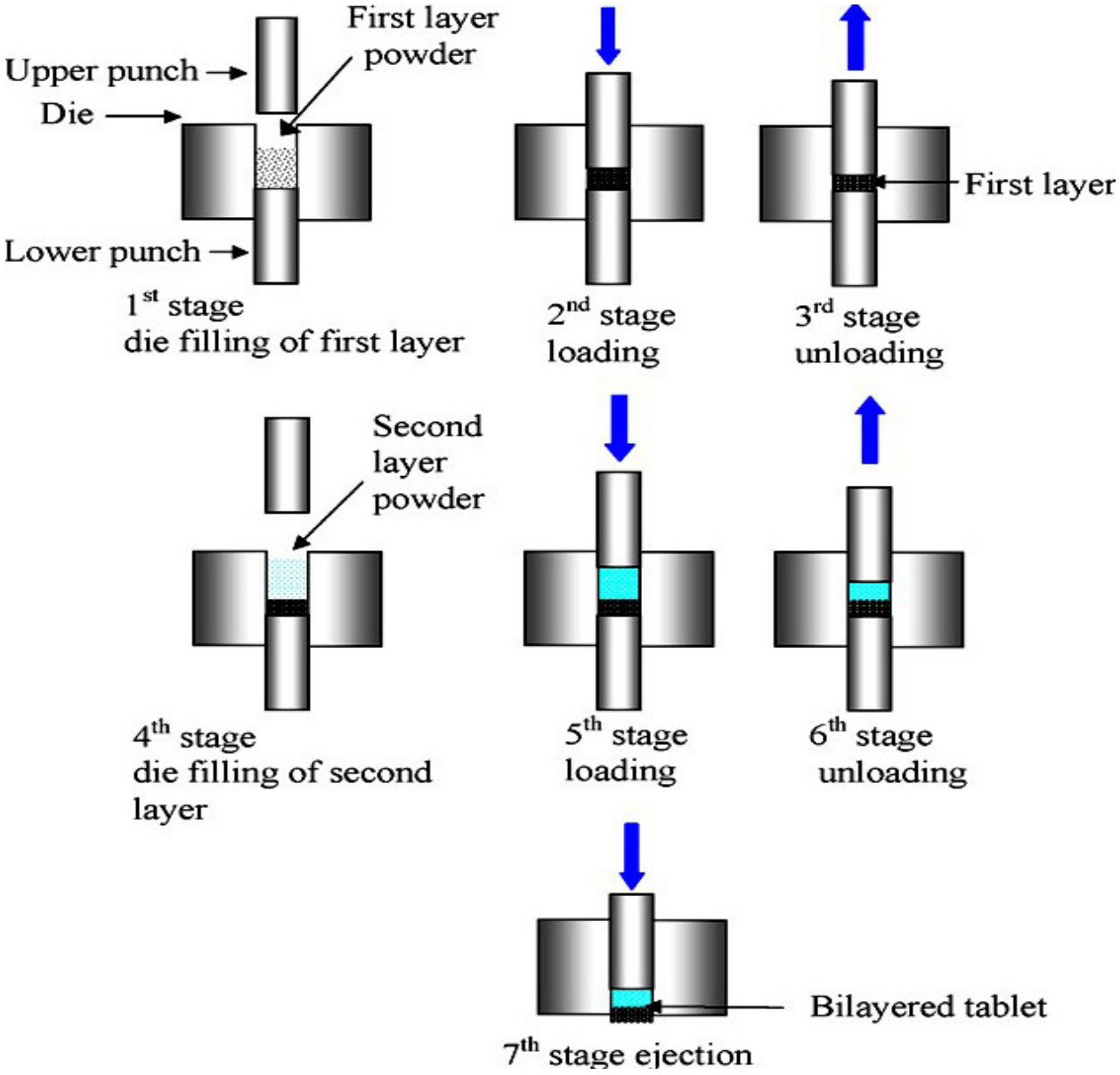

Fig No: 2 Compression Process of bilayered tablets

QUALITY AND GMP-REQUIREMENTS

To produce a quality bi-layer tablet, in a validated and GMP-way, it is important that the Selected press is capable of :

1. Preventing capping and separation of the two individual layers that constitute the bi-layer Tablet.
2. Providing sufficient tablet hardness
3. Preventing cross-contamination between the two layers
4. Producing a clear visual separation between the two layers
5. Obtaining yield Accurate and individual weight control of the two layers.

These requirements seem to be obvious but are not so easily accomplished.

RECENT DEVELOPMENTS IN THE FIELD OF BILAYER TABLETS

The introduction of bi-layer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients and incorporation of incompatible active ingredients into the single unit dosage form. Large number of work has been done in this field. Some of the recently developed bilayered tablets presented table-1.

Table No 1: Various Advancements in the Field of Bilayer Tablets[9]

DRUG(S)	DOSAGE FORM	RATIONALE
Diclofenac, Cyclobenza-prine	Bilayer tablets	Synergistic effect in pain
Granisetron HC1	Bi-layer tablets	To overcome bioavailability problem, reducing side effects
Metformin HC1, Glimipiride	Bilayer tablets	Synergistic effect in diabetes
Indomethacin	Bi-layer floating tablets	floating tablets Biphasic drug release
Metformin HC1, Atorvastatin Calcium	Bi-layer tablets	To develop polytherapy for the treatment of

		NIDDS & hyperlipidemia
Cefixime Trihydrate, Dicloxacilline Sodium	Bilayer tablets	Synergistic effect in bacterial infections
Piracetam, Vinpocetin	Bilayer tablets	Synergistic effect in Alzheimer disease
Metformin HCl, Pioglitazone	bilayer tablets	Synergistic effect in diabetes mellitus
Atenolol	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration
Cefuroxime Axetil ,Potassium Clavulanate	Bilayer tablets	Synergistic effect against microbial infections and to minimize dose dependent side effects
Amlodipine Besilate ,Metoprolol Succinate	Bilayer tablets	Synergistic effect in hypertension
Diclofenac Sodium, Paracetamol	Bilayer tablets	Synergistic effect in pain
Ibuprofen, Methocarba-mol	Bilayer tablets	Synergistic effect of drugs in back pain
Atorvastatin	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration

Atorvastatin, Calcium	Bilayer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration
Paracetamol, diclofenac	Bilayer tablets	Synergistic effect of drugs in pain
Losartan	Bilayer tablets	Biphasic release profile
Metformin HCl, Pioglitazone	Bilayer tablets	Synergistic effect in diabetes mellitus
Guaifenesin	Bilayer tablets	Biphasic release profile
Tramadol, Acetaminophen	Bilayer tablets	Synergistic effect of drugs in pain
Atenolol, Lovastatin	Bilayer floating tablets	Synergistic effect in hypertension and biphasic release profile
Montelukast, Levocetrizine	Bilayer tablets	To improve the stability of drugs in combination
Salbutamol, Theophylline	Bilayer tablets	Synergistic effect of drugs in asthma
Glipizide, Metformin HCL	Bilayer tablets	To avoid interaction b/w incompatible drugs
Telmisartan Hydrochlor-thiazide	Bilayer tablets	To minimize contact b/w hydrochlorothiazide & basic component of telmisartan
Amlodipine, Atenolol	Bilayer tablets	To improve the stability of drugs in combination

Ascorbic acid, Cyano-cobalamin	Double layer suppositories	To avoid interaction b/w incompatible vitamins
Rifampicin, Isoniazid	Capsule & tablet in Capsule	To avoid interaction b/w incompatible drugs
Misorostol, Diclofenac	Bilayer tablets	To minimize contact b/w drugs

1.3 CONTROLLED RELEASE DRUG DELIVERY SYSTEM[12- 15]

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered by oral conventional method in the form of tablets & capsules. Usually conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems. Sustained release[12 - 16] drug delivery system works on many different mechanisms to control the release rate of drugs. Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches.

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of Sustained drug delivery, greater attention is being paid on development of oral sustained release drug delivery systems. The goal in designing sustained release drug delivery system is to reduce

the frequency of the dosing, reducing the dose & providing uniform drug delivery. So, Sustained release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ 1-3. Sustained release dosage forms provide better control of plasma drug levels, less

. Hydrophilic polymer matrix is widely used for formulating an Sustained dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in blood plasma. The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell when in contact with aqueous solution and form a gel layer on the surface of the system. When the release medium is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since matrix swelling lengthens the diffusion path. It has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms. The presence of water decreases the glass transition temperature (Tg) (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain favors the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. The main polymers used in hydrophilic matrices are hydroxyl propyl methyl cellulose (HPMC) and Hydroxyl propyl cellulose (HPC), Xanthan gum, Carbopol and Alginates. The Sustained release drug delivery system is very helpful in increasing the efficiency of the dose, safety of dose as well as the patient compliance. Nowadays, the oral route of administration for Sustained release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance. The design of oral Sustained release drug delivery system depends on various factors like, physic-chemical properties of drug, type of delivery

system, disease being treated, patient condition, treatment duration, presence of food, gastrointestinal motility and co-administration of other drugs. From the above discussion, we can concluded that Moreover; the reasonable cost of oral Sustained release drug delivery system has lead ease of market penetration as replacement of oral conventional drug release rate and the proportion of total drug that can be incorporated into a matrix.

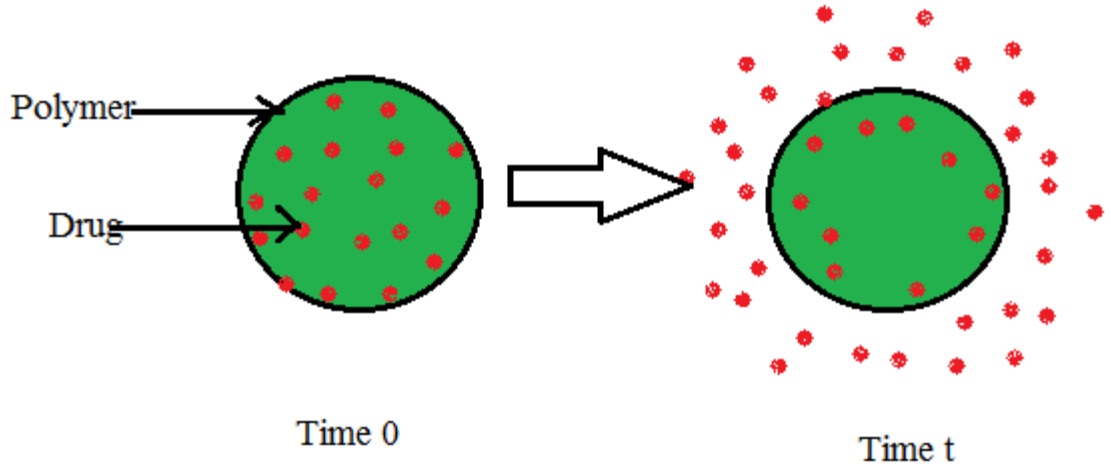

Fig No: 3 Sustained Release Of Drugs Through Matrix Diffusion.

Controlled release VS. Sustain release;[17]

Difference between controlled and sustained release is that controlled is perfectly zero order release that is, the drug is irrespective of concentration. on other hand, sustain release implies slow release of drug over the time period. It may or may not be controlled release.

Limitations of oral conventional dosage form

1. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication in narrow therapeutic index drug.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition impossible

Advantages of Sustained/Controlled release drug delivery[18,19] system over the conventional dosage form;

1. Reduced dosing frequency.
2. Dose reduction.
3. Improved patient compliance.
4. Constant level of drug concentration in blood plasma.
5. Reduced toxicity due to overdose.
6. Reduces the fluctuation of peak valley concentration.
7. Night time dosing can be avoided.

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2. LITERATURE REVIEW

Durga Prasad Pattanayak et al(2011) Attempted to design a formulation to improve the oral therapeutic efficacy with optimal control of plasma drug level which contains two ant diabetic drugs i.e. Metformin HCl and Glimepiride[20]. Bilayer tablet formulation has been developed consisting of two drug containing layers which comprises Metformin sustained release layer and an immediate release layer of Glimepiride was optimized separately and constituted in bilayer tablet, a common analytical method for quantitative combined drug

estimation was employed and evaluated. Two different matrix formulations were developed, one matrix layer with hydrophilic swellable polymer and another with hydrophobic polymer as carriers for sustained drug delivery from matrices and were evaluated. Hydroxyl propyl methylcellulose and Polyethylene oxide was used as polymers in order to get the sustained release profile over a period of 24 h. Tablets were evaluated for physical properties; drug content and in vitro drug release were compared with standard commercial tablets (Glimy-M). The excipients used in this formulation did not alter physicochemical properties of drug, as tested by HPLC, DSC, and FTIR. Stability of the drug release profiles at 6 months in 40◦C and 75%RH suggesting that HPMC based sustained release formulation was stable than the Polyethylene oxide sustained release formulation due to its stable and better targeting profile in terms of drug release. This formulation also exhibited the best fitted formulation into zero order kinetics and non-Fickian transport of the drug from the tablets was confirmed. Bilayer tablet prepared from optimized formula was found to be best suited method for fixed dose combination of sustained release Metformin HCl and immediate release Glimepiride.

S.Brito Rajet al (2011), Bilayered tablet of Metformin hydrochloride (SR) with Metoprolol tartarate[21] (IR) as a once daily formulation. The formulations of tablets (B1- B10) were prepared by using release retarding agents like HPMC K100, Eudragit S 100 for sustained release (SR) layer and super disintegrants like Crosspovidone Sodium starch glycolate (SSG) for immediate release (IR) layer. Both sustained and immediate release granules were evaluated for flow property. Bilayer tablets were evaluated for weight variation, hardness, thickness, swelling index and *in-vitro* drug release for 12 hours. All the formulations obey Zero order release kinetics and the mechanism of drug release was found to be non fickian diffusion by fitting the data to peppas equation. The result suggest that the developed Bilayer tablet of Metformin hydrochloride (SR) with Metoprolol tartarate (IR) could perform therapeutically better and improve efficacy than conventional dosage forms, and also it trounce the severe diabetic complication especially hypertension.

Rikin Patel et al (2013). Validated process of preparation of bilayered tablets of Metformin hydrochloride and Glimipride[22].Three process validation batches of same size, method, equipment and validation criteria were taken. The critical parameters involved in sifting, granulation (dry mixing, wet mixing, drying, milling, lubrication), pre compression and

compression were identified and evaluated. Different stages of manufacturing process were evaluated for acceptable granulation process and moisture content of granules after granulation; acceptable moisture content after drying; acceptable particle size distribution, blend uniformity, bulk density after lubrication; weight variation, thickness, hardness, %friability, dissolution, disintegration after compression. The outcome indicated that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes. So, manufacturing process of Metformin HCl[30] and Glimepiride bi layer tablet was considered as validated.

G. Hemanth Kumar et al (2012) Formulated and evaluate bilayer tablets of Metformin Hydrochloride and Sitagliptin Phosphate as fixed dose combination tablets for effective treatment of type II diabetes mellitus[23]. Preformulation studies including drug excipient compatibility were conducted for both drugs. Different formulations of sustained release, floating Metformin Hcl tablets were prepared by using hydrophilic polymers like HPMC K100 and Sodium CMC and were evaluated. Sitagliptin immediate release formulations were prepared using crosspovidone, croscarmellose sodium and sodium starch glycolate as superdisintegrants and were evaluated. Based on the in vitro dissolution data F7 and S9 were selected as the best formulations from Metformin and Sitagliptin formulations respectively. Bilayer tablets were prepared by slightly compressing Metformin layer (F7) and then final compression was made by placing Sitagliptin layer (S9) layer on it with final hardness 6.5 kg and they were evaluated. From the bilayer tablet Sitagliptin layer disintegrated in 52 sec, Metformin layer started floating after 5.2 min and gave total floating time 18-24 hrs with good swelling index, good post compression parameters. In vitro dissolution study of bilayer tablet was done in USP type II along with UV spectrophotometer gave cumulative % drug release of Sitagliptin as 99.15% at 30 min and 97.65 % of Metformin at 12 hrs. From the study it was found that, combination of HPMC K100 and Sodium CMC gave good sustained release for 12 hrs. Among the 3 superdisintegrants used sodium starch glycolate showed good disintegration of sitagliptin layer.

Vyas Jigar et al (2013) Bilayered gastro-retentive tablet containing MetforminHCl and Pioglitazone HCl for treatment of type-II diabetes mellitus was formulated[24] . To make the system more effective, combination of immediate layer, PioglitazoneHCl 15mg and sustained release layer of Metformin HCl 500mg were prepared. The core tablet of MetforminHCl was

prepared by using different swellable polymers like HPMC E15, HPMC K100 and carbopol by wet granulation method and evaluated for swelling index, total floating time and floating lag time. *In vitro* release studies were carried out with 0.1N HCl using USP dissolution apparatus 2 (paddle). Tablet thus formulated using HPMC K100M and E15 provided sustained release of Metformin HCl over a period of 10 hours. The immediate release layer of PioglitazoneHCl was prepared by using crosspovidone, a super disintegrant by direct compression method and evaluated for disintegration time and dissolution also. Then bilayered tablet was prepared with the selected core tablet batch of MetforminHCl followed by compression coating with the selected immediate release layer of PioglitazoneHCl. The present study concluded that bilayered tablet can be a good way to treat diabetic patients with combination therapy.

Gundaraniya PV et al (2013) Developed bilayer tablets containing sustained release microspheres as one layer and immediate release as another layer[25]. The proposed dosage form is intended to decrease the dosing frequency and the combined administration of an anti-diabetic agent. Several pharmaceutical companies are currently developing bi-layer tablets, for a variety of reasons: patent extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop and produce such tablets. One such approach is using microspheres as carriers for drugs also known as micro particles. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest. Microspheres received much attention not only for prolonged release, but also for targeting of ant diabetic drugs. Bilayer tablet via microsphere is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Especially when in addition high production output is required. An attempt has been made in this review article to introduce the society to the current technological developments in bilayer and floating drug delivery system.

Ananda Kumar Chettupalli et al (2013) developed a bi layer tablet of immediate release Pioglitazone and controlled release Metformin Hydrochloride, which is used as an Anti-hyperglycemic agent[26]. Metformin Hydrochloride has biological half-life nearly about 6 hours, so, an attempt was made in the direction of preparation and optimization of a combination of Sustained release and immediate release in a single tablet. In controlled release layer natural gums like xanthum gum, gum trgacanth and guar gum were used as retarding materials and in

immediate release layer cros carmellose sodium was used as a super disintegrent to give the faster release of pioglitazone. The tablets were prepared by wet granulation method and by direct Compression. Granules were evaluated for pre compression parameters and the tablets were evaluated for post compression parameters.

Pamu. Sandhya et al (2014) Prepared bilayer tablets of Glimepride and Metformin HCL in combination[27]. Metformin hydrochloride and Glimepiride are oral hypoglycemic drug and effectively used in treatment of diabetes mellitus (type-2 diabetes). The main aim of the present study was to formulate Metformin hydrochloride[37] sustained release and Glimepride immediate release matrix tablets as a dosage form by different polymers such as HPMC, Povidone, Lactose Monohydrate, Ethyl cellulose, Microcrystalline Cellulose and study the *invitro* release patterns of the drug. In the present study bilayer tablets Glimepride prepared by direct compression method and Metformin prepared by wet granulation technology. The prepared tablets were evaluated for various physicochemical parameters such as drug-excipient interaction by FTIR, flow properties, hardness, weight variation, friability, and in vitro dissolution studies optimized based on desired sustained release time (16hrs) and acceptable floating properties The FTIR study revealed that there is no drug-excipient interaction. During preformulation it has been observed that there is no drug- drug and drug excipient interaction, so the excipients which have been selected for the formulation are compatible with the drugs. This system provides zero order or near zero order release for IR layer and SR layer provides Higuchi model.

Goswami, Laxmi et al (2011) Dealt with the formulation and evaluation of combined floating controlled drug delivery system using Metformin hydrochloride along with Pioglitazone hydrochloride as a bilayer tablet formulation for prolonged gastric residence time[28]. Metformin and pioglitazone hydrochloride has been used as an oral hypoglycemic agent for control of diabetes. The fabrication of bilayer floating tablet was done by modified direct compression using polymer like hydroxypropylmethyl cellulose (HPMC), carbopol, polyvinyl pyrrolidone to facilitate immediate release of pioglitazone and sustained release of metformin. The formulated tablets were subjected to various evaluation parameter including floating lag time, floating duration, drug content and spectrophotometric simultaneous estimation. The in-vitro dissolution studies were performed by USP-II type dissolution apparatus in 900ml 0.1(N) HCl medium (pH-

1.2) at 50 rpm and 37±0.5°C. Formulated tablets remain buoyant over a period of 12-20 hrs and released more than 80% of drug in study period.

JYOTSNA GODBOLE et al (2012) Designed the concept of bilayer matrix tablets containing Acarbose as immediate release component using sodium starch glycolate and cross carmillose sodium as super disintegrates and Metformin hydrochloride (HCl) for sustained release by using hydroxyl propyl methyl cellulose (HPMC K 4M), (HPMC K 100) and sodium carboxyl methyl cellulose (SCMC) as the matrix forming polymer and PVPK-30 as binder[29]. Matrix tablet are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both as well as diffusion controlled mechanisms metformin HCl is 6.2 hrs, so an attempt was made in the direction of preparation and optimization of a combination of sustained release and immediate release in a single tablet. Tablets were prepared by wet granulation and direct compression method. Tablets were evaluated for post compression parameters. The tablets were evaluated for physico-chemical property. All the values were found to be satisfactory. Invitro release studies were carried as per USP in water and phosphate buffer of pH 6.8 using the apparatus I. The final preparation showed release of drug up hours. FTIR studies revealed that there is no interaction between the drug and other excipients used in the study.

Chantal Mathieu and Evy Degrande et al (2008).Carried out an extensive clinical program involving approximately 22,000 patients and 7000 patient-years of exposure to vildagliptin has shown that the agent is well tolerated and efficacious in improving glycemic control in patients with type 2 diabetes mellitus (T2DM)[30]. Monotherapy trials have shown that significant HbA1c lowering is accompanied by body weight-neutral and lipid-neutral effects, low risk of edema, and low risk of hypoglycemia. These characteristics make vildagliptin a favorable partner for combination therapy. Studies of vildagliptin as an add-on to metformin have shown significant improvements in glycemic control (comparable to that of thiazolidinedione add-on), with the combination being well tolerated and associated with low risks for hypoglycemia and adverse effects on weight or lipid levels. Good tolerability and clinically relevant improvements in glycemic control have also been observed with vildagliptin as an add-on treatment to sulfonylurea, thiazolidinedione, or insulin treatment or in initial combination treatment with pioglitazone. Improved β-cell function and glycemic control have been shown with vildagliptin

in subjects with impaired glucose tolerance and in T2DM patients with mild hyperglycemia, with some evidence in the latter suggesting the potential for modifying disease course.

James E. Signorovitch, et al (2011) Aimed at comparing 12-week glycaemic control with vildagliptin 50 mg twice daily versus sitagliptin 50 or 100 mg once daily in Japanese patients with type 2 diabetes[31]. Two trials of vildagliptin and three trials of sitagliptin were identified for Japanese patients. Across all included trials, a total of 264 patients were treated with vildagliptin 50 mg twice daily, 235 were treated with sitagliptin 50 mg once daily and 145 were treated with sitagliptin 100 mg once daily. Mean baseline HbA_{1c} ranged from 7.4% to 7.8% per trial. Before matching, significant ($p<0.05$) cross-trial differences included lower mean HbA_{1c} (by 0.2–0.3%) and higher FPG (by 5–13 mg/dl in vildagliptin trials. After matching, all baseline characteristics were balanced between treatment groups. Combining matched trials, vildagliptin 50 mg twice daily was associated with significantly greater absolute HbA_{1c} reduction by 0.28% compared with sitagliptin 50mg once daily (95% CI 0.15, 0.41; $p<0.001$) and by 0.35% compared with sitagliptin 100mg once daily (95% CI 0.07, 0.62; $p = 0.013$). After adjusting for baseline differences among trials of vildagliptin and sitagliptin in Japanese patients with type 2 diabetes, vildagliptin 50 mg twice daily was associated with significantly greater HbA_{1c} reduction than sitagliptin 50 mg or 100 mg once daily.

Ashutosh Kumar et al (*2012)* formulate and evaluate the bilayer tablet containing Metoprolol succinate as sustained release and Ramipril as an immediate release layer32. The sustained release32 part was formulated by using hydrophilic polymer HPMC K - 100 and HPMC K4M. HPMC K4M was kept constant in a concentration of 10% for 5 formulations and 0.7% was increased in case of the 6th formulation. Metoprolol succinate is a beta 1-selective (cardio selective) adrenoceptor blocking agent its chemical name is (I) - (isopropyl amino) -3-(p-(2methoxy ethyl) phenoxyl)-2-propanol succinate & Ramipril is a 2-aza-bicyclo [3.3.01-octanc-3-carboxylic acid derivative. It is a white, crystalline substance soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105°C and 112°C.Ramipril chemical name is (2S, 3aS, 6aS)-l [(S)-N-[(S)-l-Carboxy-3-phenylpropyl] alanyl] octahydrocyclopenta [b]pyrrole-2-carboxylic acid, 1-ethyl ester. In the Sustained Release formulation F6, using HPMC K100 56.7% and HPMC K4 M 10.7% gives the drug release of 15.6%, 34.9%, 54.19%, 80.25 %, 95.5% at IST, IVth, VIIIth and XXth hour respectively. As the

polymer ratio increases the release rate of the drug decreases from the matrix tablet formulation is various physiological pH conditions. All the tablet formulations were evaluated for their characteristics such as hardness, thickness, diameter, friability, weight variation and content uniformity (assay). From the investigation it was noted that the drug content were found to fall within the limits. From this study it can concluded that Ramipril and Metoprolol can be formulated with Metoprolol as sustained release layer by using HPMC K -100. The release can be so well controlled that it almost coincides the theoretical release pattern for the drug by proper adjustment of polymer ratio. Ramipril is formulated as one layer as immediate release. Hence this dual release formulation designed was found to be quite useful in combination therapy

3. SCOPE, OBJECTIVES AND PLAN OF WORK

Glucose lowering by anti diabetic drug in the diabetic management cannot be maintained over a long period of time with the use of conventional dosage forms. Also probability of plasma level fluctuation and missed dosages is higher.

Two or more drugs from pharmacological action are needed to achieve adequate blood glucose control. single dose combination anti diabetic therapy is an important option that combines efficacy of blood glucose reduction and low side effect profile with convenient once daily dosing to enhance the compliance. Because of the lower dose of anti diabetic drug, metabolic and clinical events are decreased. The primary aim of treatment is to lower blood glucose to a normal level using whatever combination of drug that achieves the goal.

The rationale for using fixed dose combination therapy is to improved blood glucose control. Employing two anti diabetic drug can also minimize the clinical and metabolic effects that occur with maximal dosages of individual components of the combined tablet. This has potential advantage as suggested some investigation have recommended using combination anti diabetes therapy as initial therapy as initial treatment, particularly in patients with target organ damage or more severe initial level of diabetes,

To reduce the frequency of administration and improve the patient compliance a once daily sustained release formulation is desirable. The most commonly used method of controlling the drug release includes the drugs in a matrix system. Because of their flexibility hydrophilic polymer matrix system are widely used in oral controlled drug delivery to obtain desirable drug release profile, cost effectiveness, and regulatory acceptance.

AIM OF WORK

To develop once novel daily bilayer tablet of metformin hydrochloride as a sustained release, vildagliptin as immediate release.

The bilayer tablet containing sustains release part and immediate release part is administered, the immediate release part is used to achieve therapeutic level immediately and it act as a loading dose. The sustained part releases the drug for prolonged period and act as the maintenance dose.

Metformin hydrochloride the hepatic glucose production, decrease the intestinal absorption of glucose and improve the insulin sensitivity by increasing the peripheral glucose uptake and utilization. the maintenance the constant plasma level of anti diabetic drug is important in ensuring the desire therapeutic response. It reduces the blood glucose by reduction of insulin level and maintains the blood glucose level. Vildagliptin inhibits dipeptidyl peptidase-4 (DPP-4). This in turn inhibits the inactivation of GLP-1 by DPP-4, allowing GLP-1 to potentiate the secretion of insulin in the beta cells. Dipeptidyl peptidase-4's role in blood glucose regulation is thought to be through degradation of GIP and the degradation of GLP-1

OBJECTIVES

1, To develop the SR matrix tablet formulation of Metformin hydrochloride.

2, To develop the IR tablet of vildagliptin.

3, To access the release patterns of both the drugs from a bilayer tablet (super dosage form).

PLAN OF WORK

LITERATURE REVIEW

PROCUREMENT OF DRUG AND EXCIPIENTS

PREFORMULATION STUDIES

FORMULATION DEVELOPEMENT

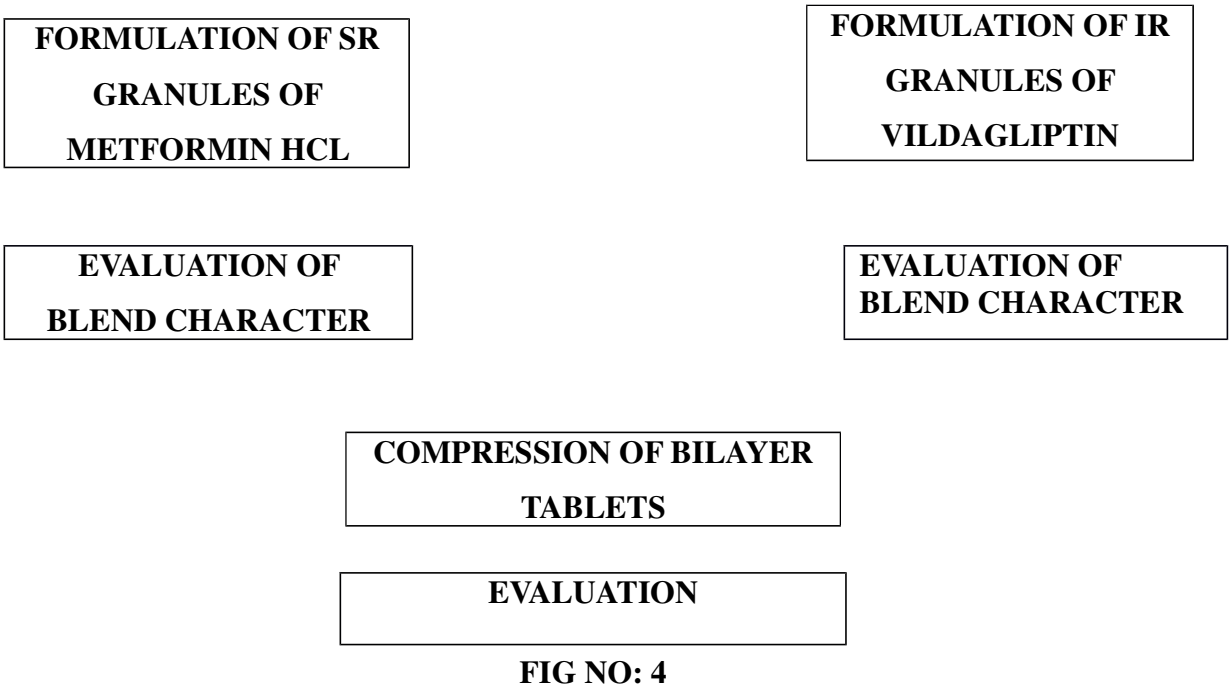


FIG NO: 4

PLAN OF WORK

1,Preformulation studies on drugs .

2, Calibration of metformin and vildagliptin by HPLC

3. Formulation development of SR containing metformin hydrochloride of bi layer tablet, to achieve programme sustained release

4. Formulation development of IR part containing vildagliptin of bi layer tablet.

5. Compression of bilayer tablet.

6. Evaluation of bilayer tablet for

   a. Weight variation

   b. Friability

c. Thickness

d. Disintegration

e. Drug release.

4. MATERIALS AND METHODS

4.1,MATERIALS USED

The following materials obtained from commercial sources were used for the formulation of bilayer tablets

Table No: 2

S.NO	MATERIAL	SOURCE
1	Metformin hydrochloride	Chiplun fine chemicals. Mumbai
2	Vildagliptin	Gift samples from Novaties pharma. Mumbai
3	Hydroxyl propyl methyl cellulose (Methocel K-100 MCR)	S.D.fine chem...ltd. Mumbai
4	Cross Carmellose sodium	Loba Chemical.pvt ltd .India
5	Micro crystalline cellulose PH 102	Samsung fine Chemicals. Mumbai
6	Lactose BP(supertab 30 GR)	Fisher ltd. Chennai
7	Sodium Starch glycollate	Gift samples from FDC pharma, Maharashtra.
8	Magnesium stearate	Jain enterprises. Chennai
9	Hypromellose (methocel E 15 cps)	S.D. fine chemicals .Mumbai

4.2 INSTRUMENTS USED

The following materials were obtained from commercial used for the formulation of bilayer tablets **Table No: 3**

S NO	EQUIPMENTS	SOURCES
1	28 station double hopper bilayer press	Cadmach, Mumbai
2	Rapid mixture granulator	Remi,Mumbai
3	Double cone blendor	Cadmach.Mumbai
4	Hardness tester	Monosanto
5	Friability tester	Electro lab Chennai
6	Disintegration apparatus	Electro lab . Chennai
7	Dissolution apparaus	Electro lab .Chennai
8	Weighinig balance	Precisa, Mumbai
9	HPLC/SPD 10 AVP	Shimaldu. JapanI
10	Uv spectrophoto meter	Shimaldu. japanI
11	pH meter	STL ltd. Chennai
12	refrgerator	Whirlpool india.ltd.chennai
13	Vernier caliper	Mututoyo, Goa
14	Sonicator pk 106	Bandelin sonorex, Mumbai
15	Sieves 30#,20#,40#	Bio hem.. Pvt ltd. Mumbai
16	Vibro sifter	Janath pharmaceutical, Mumbai
17	Tab density tester	Electro lab, Chennai

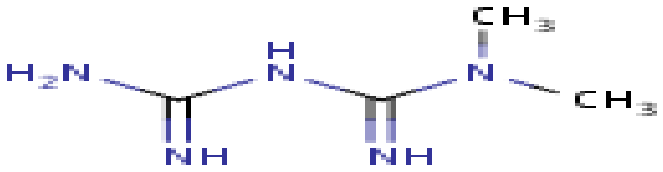
4.3. DRUG PROFILE

4.3.1. METFORMIN HYDROCHLORIDE[33,34]

Functional category

Metformin hydrochloride is an anti diabetic drug from the bigunaide class of oral anti hyperglycemic agents

Structure



Class :Guanidines
Subclass :Biguanides
Chemical name **:** -(diamino methylidine)-3,3-dimethyl-gunadine1

Molecular Formula: C4H12ClN5

Molecular weight **:** 165.63gm/mol

Iupac name **:** N-N-dimethylimidocarbonimidic diamide hydrochloride

Category **:** Anti diabetic agent

Description **:** white to off white crystalline powder, odourless

PKa **:** in acid :12.4

Solubility **:** freely soluble in water, slightly soluble in alcohol,
Practically insoluble in acetone and in methylene chloride

Half life **:** 6.2 hours. Duration of action is 8-12 hours.

Pharmacokinetics[35, 36]

Absorption and Bioavailability

- The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions
- approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg,
- 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses,
- This is due to decreased absorption rather than an alteration in elimination.

.

Metabolism and Elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged

in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans)

nor biliary excretion. Renal clearance (see Table 1) is approximately 3.5 times greater than cre atinine

Pharmacodynamics

Metformin is an oral anti hyperglycemic agent that improves glucose tolerance in patients with NIDDM, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other class of oral anti hyperglycemic agents. Unlike sulfonyl ureas, metformin does not produce hypoglycemia in either patients with NIDDM or healthy subjects and does not cause hyper insulinemia. Metformin does not affect insulin secretion.

Pharmacology

Mechanism of action[34]

Metformin's mechanisms of action differ from other classes of oral antihyperglycemic agents. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by metformin of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. Metformin administration also increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake. The rare side effect, lactic acidosis, is thought to be caused by decreased liver uptake of serum lactate, one of the substrates of gluconeogenesis. In those with healthy renal function, the slight excess is simply cleared. However, those with severe renal impairment may accumulate clinically significant serum lactic acid levels. Other conditions that may precipitate lactic acidosis include severe hepatic disease and acute/decompensated heart failure.the mechanism of action of metformin presented in fig no:5

ADVERSE REACTION

Adverse reactions of a more intense character including epigastric discomfort, nausea, and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen.

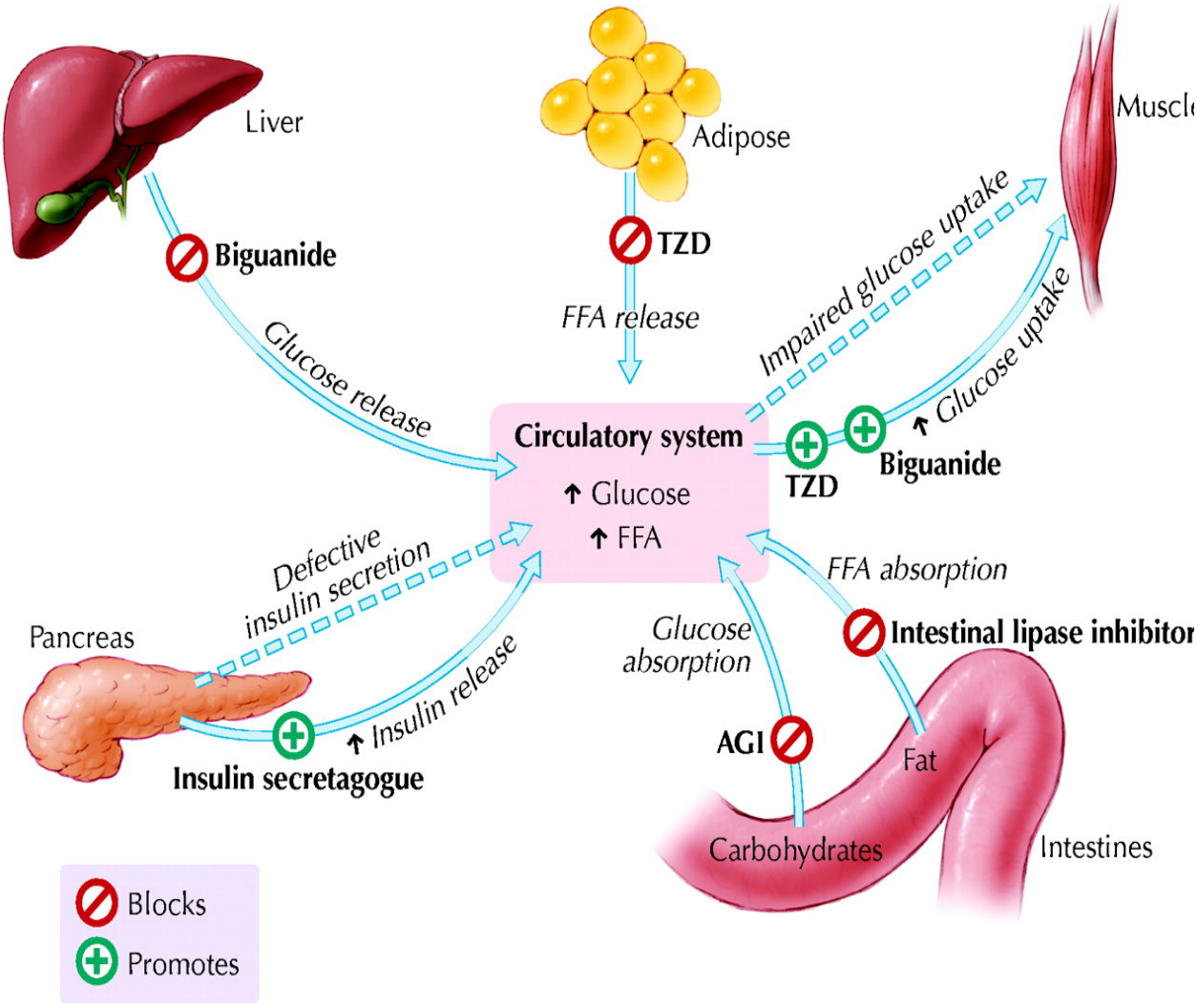
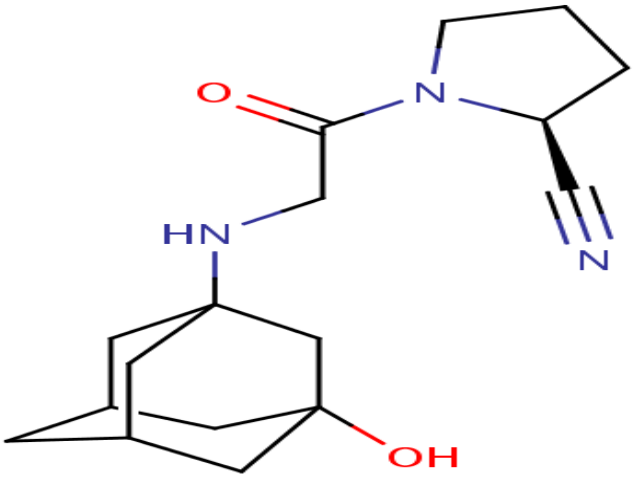


Fig No:5 Mechanism of action of Metformin

4.3.2 .VILDAGLIPTIN[37]

Chemical name: 1-[(3-Hydroxy-adamant-1-ylamino)acetyl]-pyrrolidine-2(S)-carbonitrile

Chemical structure:



Molecular formula ; $C_{17}H_{25}N_3O_2$

Molecular weight : 303.40

DESCRIPTION

Vildagliptin is a white to slightly yellowish or slightly greyish crystalline powder with a melting point/range of approximately 150oC. It is freely soluble in water.

PHARMACOLOGY[38]

Pharmacodynamics

Vildagliptin belongs to a class of orally active antidiabetic drugs (DPP-IV inhibitors) that appear to have multiple functional benefits beyond simple blood-glucose control. One of these is a potential protective effect on pancreatic beta cells, which deteriorate in diabetes. Vildagliptin

appears to be safe, very well tolerated, and efficacious. Following a meal, gut incretin hormones are released. The most important incretin hormones are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). These hormones, secreted in the human small intestine, are responsible for insulin release due to increased glucose levels. In contrast to agents that promote insulin secretion via glucose-independent mechanisms, GLP-1's dependence on glucose concentration is considered beneficial due to a lower risk of hypoglycemia. GLP-1 also inhibits glucagon secretion and increases beta cell mass by stimulating proliferation and neogenesis. However, the clinical utility of GLP-1 is limited by its short half-life (2 minutes). GLP-1 is rapidly degraded by the proteolytic enzyme DPP-IV. To enhance GLP-1 activity, inhibition of the DPP-IV enzyme is emerging as a novel therapeutic approach in the treatment of diabetes. Administration of vildagliptin enhances GLP-1's ability to produce insulin in response to elevated concentrations of blood glucose, inhibit the release of glucagon following meals, slow the rate of nutrient absorption into the bloodstream, slow the rate of gastric emptying, and reduce food intake

Absorption

Rapidly absorbed following oral administration with an oral bioavailability of greater than 90%

Distribution

The plasma protein binding of vildagliptin is low (9.3%), and vildagliptin distributes equally between plasma and red blood cells

half life : The elimination half-life is approximately 90 minutes

MECHANISM OF ACTION

Vildagliptin inhibits dipeptidyl peptidase-4 (DPP-4). This in turn inhibits the inactivation of GLP-1 by DPP-4, allowing GLP-1 to potentiate the secretion of insulin in the beta cells. Dipeptidyl peptidase-4's role in blood glucose regulation is thought to be through degradation of GIP and the degradation of GLP-1(fig no:6)

FIG NO: 6 MECHANISM OF ACTION OF VILDAGLIPTIN

VILDAGLIPTIN

Mixed meal

Intestinal release of GLP-1

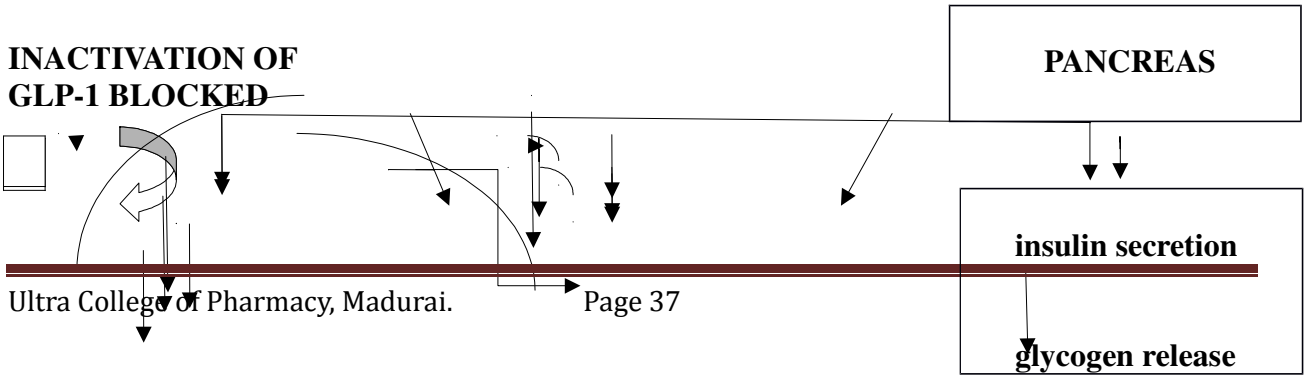
INHIBITION DPP-4

Active GLP-1

DPP-4

INACTIVE GLP-1

INACTIVATION OF GLP-1 BLOCKED



4.3.3. EXCIPIENTS PROFILE

Table No 4: EXCIPIENTS PROFILE[40, 39]

S NO	EXCIPIENTS	PROPERTIES	USES
1	MICRO CRYSTALLINE CELLULOSE BP(PH 102)	Fine or granular, white, odourless In Soluble in water, slightly soluble in Noah, PH Between 5-7.5	Suspending agent,adjuvant
2	LACTOSE BP(SUPER TAB 30 GR)	white, odourless, crystalline powder, freely but slowly soluble in water, practically insoluble in ethanol	Pharmaceutical aid
3	SODIUM STARCH GLYCOLLATE	Very fine, white or off white, odourless, practically in soluble in water ,insoluble most organic solvents	Pharmaceutical aid(tablet disintegration)
4	MAGNESIUM STERATE	Colourless crystals or white, odourless, very soluble in boiling water, practically insoluble in ethanol,	Pharmaceutical aid (lubrication)
5	HYPROMELLOSE(Methocel K-100 MCR) HYPROMELLOSE(Methocel E 15 CPS) (HYDROXY PROPYL METHYL CELLULOSE)	White or yellowish white, fibrous or granular powder, odourless, practically insoluble in hot water, acetone, ether, toluene.	Pharmaceutical aid (tablet excipients, suspending agent)
6	CROSS CARMELLOSE SODIUM	White or almost white,	Pharmaceutical

		odourless , practically insoluble in acetone ,ethanol, toluene and ether, easily dispersed in water.	aid(Suspending agent, viscosity increasing agent, excipients)

5 .METHODS (EXPERIMENTAL)

5.1 SIMULTANENEOUS ESTIMATION OF VILDAGLIPTIN AND METFORMIN HYDROCHLORIDE

The analytical method followed was HPLC which is as follows.

ASSAY:

Equipment : HPLC

Column : intertsil ODS-3VC18,150 mm X 4.6mm,5µm or equivalent

Wavelength : 260 nm

Temperature : ambient

Flow rate : 1.0ml/min

Injection volume : 20µ/ml

Run time : about 10 min

Mobile phase : filtered and degassed mixture buffer, acetonitrile; buffer (40;60v/v)..

Buffer: Dissolve 2.87gm of potassium di hydrogen phosphate in 300 ml water, dilute 1000 ml with water and adjust to the pH to 7.0 with sodium hydroxide.

Diluents: pH 6.8 buffer

Standard preparation:

1, Dissolve about 16 mgm of vildagliptin phosphate in 10 ml dissolution medium, dissolve and dilute to 50 ml mobile phase.

2, Dissolve about 125 mgm of metformin hydrochloride in 10 ml of mobile phase, and dilute 50 ml of mobile phase. Further take 5 ml solution (1) and (2) in50 ml volumetric flask, make up the mobile phase to 50 ml. filter the solution through 0.45micron membrane filter.

Sample preparation:

Weigh and powder 20 tablets take 250 mg equivalent of metformin hydrochloride in 10 ml of mobile phase, in 10 ml of mobile phase and dilute 100 ml with the same solvent. Further dilute five ml of 5ml with mobile phase. . Filter the solution through 0.45micron membrane filter

Procedure:

Inject 20 µl volumes of blank, standard and sample preparation and record the peak response for major peaks.

Chromatograph the standard preparation, sample preparation and record the peak responses directed under the procedure. The test is not valid unless.

a) The theoretical plates for of metformin hydrochloride peak in standard preparation are not less than 2000.
b) The tailing factor of metformin hydrochloride peak in standard preparation is not more than 2.0

c) The relative standard deviation for six replicate injection of standard preparation is not more than 2.0%

For vildagliptin

calculate the mg vildagliptin from the declared content of vildagliptin phosphate using the following expression

$$\frac{AT}{AS} \times \frac{WS}{50} \times \frac{5}{50} \times \frac{100}{WP} \times \frac{50}{5} \times \frac{P}{100} \times AVG.WT$$

Where,

AT = Area of vildagliptin in sample preparation

AS = Area of vildagliptin in standard preparation

WS = weight of vildagliptin working standard in mg

WP = weight of vildagliptin working sample in mg

P =purity of vildagliptin phosphate on unhydrous basis

407.32 and 523.32 are the molecular weight of vildagliptin and vildagliptin phosphate.

= mg content of vildagliptin

= mg/label claim x100

= % content of vildagliptin

For metformin hydrochloride

Calculation; calculate the mg metformin hydrochloride and vildagiliptin in the tablet form the following expression =

$$\frac{AT}{AS} \times \frac{WS}{50} \times \frac{5}{50} \times \frac{100}{WP} \times \frac{50}{5} \times \frac{P}{100} \times AVG.WT$$

= mg content of metformin hydrochloride

= mg/lable claim x100

= % content of metformin hydrochloride

Where,

AT = Area of metformin hydrochloride in sample preparation

AT = Area of metformin hydrochloride in standard preparation

WS = weight of metformin hydrochloride working standard in mg

WP = weight of metformin hydrochloride working standard in mg

P = purity of metformin hydrochloride working sample in mg

5.2 FORMULATION DEVELOPMENT

PREPARATION OF BILAYER TABLETS

1, PREPARATION OF VILDAGLIPTIN IR GRANULES

The formula followed is given in table 5

Table No: 5

S No	Name of the ingredients	Quantity (mg)
	Blendings:	(for 1 tablet)
1	vildagliptin	50.0
2	Microcrystalline cellulose BP(PH 102)	84.2
3	Lactose BP (super tab GR)	47.8
4	Sodium starch glycolate BP	6.0
	Lubrication:	
5	Magnesium stearate	2.0

STEP 1 SIFTING MATERIALS

All the ingredients were weighed and metioned below according to the formula and pass through sieve no 40 #

S No	Name of the ingredients	Seiv e no
1	vildagliptin	40#
2	Microcrystalline cellulose BP(PH 102)	40#
3	Lactose BP (super tab GR)	40#
4	Sodium starch glycolate BP	40#
5	Magnesium sterate	40#

STEP 2 MIXING AND GRANULATION

1. Shifted material loaded from the step 9 was loaded in to the rapid mixer granulator

1. The materials were mixed for 20 mints
2. The granulation was continued till coherent mass was obtained.
3. The granules was unloaded in to HDPE container line with double line poly ethylene bag the container

STEP 3 SHIFTING AND MILLING

- The dry granules were shifted through sieve no 40#
- The retains granules through 0.5 mm screen

STEP 4 FINAL DRYING

The granules were dried at 60 till the LOD reached to 4.0 -5.0%

STEP 5 LUBRICATION

- Sift the magnesium stearate was shifted shifted through sieve no 40# loaded in to the blender.
- The blend was contuniued for 5 mints
- The material was blended for 15 mints

The blend was unloaded in to HDPE container line with double line poly ethelene bag . the container were tightly were closed and weighed .

CHRATERIZATION OF BLEND

EVALUATION OF FLOW PROPERTIES:-

The flow properties of granules were studied by measuring the angle of repose employing open tube method,. The angle of repose was calculated by using the following formula

$$\text{Tan } \alpha = \frac{h}{r} \text{ or } \alpha = \text{Tan}^{-1}\frac{h}{r}$$

Where h = height of the pile, cm

r = radius of the base of the pile, cm

BULK DENSITY:-

Bulk density is the ratio of the granules to the bulk volume it occupies, expressed in gm/ml. granules were weighed and poured into a 100ml- measuring cylinder and the volume was measured.

Poured bulk density = Mass of granules

Volumes packing

TAPPED DENSITY:-

Tapped density determined by weighed accurately 5 gm of the granules were weighed and poured into a 100ml-measuring cylinder and the volume was measured. It was tapped mechanically for 100 times till a constant volume bulk volume obtained, which includes the true volume of granules and void space among the granules

Tapped density = Mass of granules

Tapped volume of packing

CARR'S INDEX:-

The percentage of compressibility was determined by Carr's compressibility index**.**

Carr's index (%) = Tapped density- Bulk density × 100

Tapped density

HAUSNER'S RATIO:-

Hausner ratio s determined by comparing the tapped density to the bulk density by using the equation

Hausner's ratio = Tapped density

Bulk density

PREPARATION OF METFORMIN HYDROCHLORIDE SR GRANULES

Working formula[41,42] Table No: 6

S NO	NAME OF THE INGREDIENTS	F1	F2	F3	F4
	Dry mix				
1	Metformin hydrochloride	500	500	500	500
2	Hypromellose(methocel-100MCR)	**.....**	50	40	-
3	Carmellose sodium	**……..**	20.80	20.80	20.80
	Binder				
4	Hypromellose(Methocel E cps)	**…….**	40	25	25
5	Purified water	**…….**	q.s	q.s	q.s
	Pre-lubrication				

6	Hydroxy prophyl methyl cellulose	210	225	210	210
	Lubrication				
7	Magnesium sterate	**……**	10	10	10

STEP 1 SIFTING MATERIALS

All the ingredients mentioned blow were weighed accordingly to the formula and passed through sieve no 40#

S no	Ingredients	Sieve no
1	Hypromellose (methocel k-100MCR)	40#
2	Carmellose sodium	40#

STEP 2 MILLING

Metformin hydrochloride was milled through 2.0 mm screen with knife in for ward direction

STEP 3 PREPARATION OF BINDER

S no	Ingredients
1	Hypromellose (method E 15 cps)
2	Purified water

1,Purified water was taken in the stainless steel container and hypromellose(method E15 cps) was dissolved under constant stirring

2,The above solution was mixed with contunious stirring till homogeneous solution was obtained

STEP 4 DRY MIXING

Sifted material was changed in the mixer and milled metformin hydrochloride was added mixed in slow speed for 20 minutes.

STEP 5 GRANULATION

Binder solution was added to the main bowl of the mixer and mixed well until coherent mass was obtained.

STEP 6 DRYING

The wet granules were dried at 55 c for 30 minutes . the semi dried granules shifted through the 16#.the roughage was milled through 2.0 mm screen .

STEP 7 FINAL DRYING

/The shifted granules were dried at 80 c till the LOD was reached to 3.0 -4.0% W/W

STEP 8 LUBRICATION

1, Sifted hydroxyl propyl methyl cellulose (K -100MCR) were loaded through 40 # in to drum blender along shifted material from step 4.

- 2,The granules were blended for 20 mints in a blender.

Magnesium state was filled through 40 # and loaded in to the blender and the blender was continued for 5 mints.

The blend was unloaded in to HDPE container line with double line poly ethylene bag . the container were tightly were closed and weighed and the details were recorded.

FORMULATION DEVELOPMENT

To arive at a formula which will release metformin hydrochloride in the pattern similar data given in the table

Time	Expected cumulative % of metformin release
At the end of2hour	limit between
At the end of2hour	limit between 35-60
At the end of3 hour	limit between 45-60
At the end of4 hour	limit between 55-80
At the end of5 hour	limit between 60-85
At the end of 6 hour	limit between 75-90
At the end of 8 hour	limit between 80-95
At the end of 10 hour	limit not less than 85%

CHARACTERIZATION OF BLEND

The characterization of blend like Angle of repose, Bulk Density, Tapped Density, Hausener s ratio and Compressibility Index were performed

COMPRESSION OF BILAYER TABLET[43]

STEP 1 cleaning of compression machine

The machine has 2 hopper and all parts of machine inclouding hopper, turret, food shoe, punches, and die cavity are previously cleaned by iso propyl alcohol and dried

Step 2 fitting of B-tolling punches

The B-tolling punches are fitted in the holder and the hooper are fitted the position.Adjust the machine for its weight, hardness and thickness.

Step 3 loading of granules

The two type of granules are loaded hooper separately. The motor driven by 25 rpm. The metformin hydrochloride part is white in colour and the vildagliptin is colour

Step 4 first compression

The metformin hydrochloride part is compressed first in the cavity in sequence in the granules are lightly granules are lightly compressed and remove the air from the die cavity.

Step 5 second compression

During the second compression the second layer of colour part was deposited on the first layer. The whole is compressed in to a firm tablet in a normal way. During the compression ,weight variation, hardness, thickness, friability and disintegration test are complied.

EVALUATION OF BILAYER TABLETS

1, **WEIGHT VARIATION TEST**

Weights of individual 20 tablets noted and their mean weight is calculated, and the percentage deviation is calculated by using the formula

Percent deviation = actual value-average value/ actual value x100

the limit for weight variation is=±5%

2,THICKNESS

Select 10 tablets random and determine the individual thickness of each tablet with vernier caliper. Calculate the average thickness and record. The average thickness is given in the table.

Thickness in mm	Limits in mm
5.67	5.5±0.3(5.2 to 5.8)

3,DISSOLUTION TEST

Dissolution parameters;

Apparatus : USP Apparatus-II (paddle)

Dissolution medium : 6.8 medium

Volume : 900 ml

Speed : 75 ml

Temperature : 37±0.5 c

Time : 30 minutes

Procedure:

Place 900 ml of 6.8 medium in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37±0.5 c. place one dosage in each vessel, cover the vessel and operate the apparatus at the specified rate. After 30 minutes of operation in 6.8 medium, withdraw an aliquot of the fluid. Perform an analysis of the aliquot using a below described method.

CHROMATOGRAPHIC SYSTEM:

Column : inertsil ODS-3VC18,150mm×4.6,5µ or equivalent

Oven temperature :1.0ml/min

Detector : uv 261 nm

Injection volume : 20µl

Run time : 7 mints

Mobile phase : acetonitrile:buffer(40:60v/v. filter and degas it.

Buffer: Disodium hydrogen phosphate 28.80 gms and potassium dihydrogen phosphate 11.45 gms dissolved in water, make up 1000 ml.

Diluents: dissolution medium

Standard preparation:

1, Dissolve about 64 mgm of vildagliptin phosphate in 10 ml dissolution medium, dissolve and dilute to 100 ml mobile phase.\

2, Dissolve about 55 mgm of metformin hydrochloride in 10 ml ofdissolution medium,add 10 ml of solution (1) and make up dissolution medium with 100 ml

Sample preparation:

place one tablet in to each of the six dissolution vessel and start dissolution test.at the specified interval ,withdraw about 10 ml of the sample solution from each dissolution vessel. Filter through whatman filter paper no:41 filter and use the solution as sample solution

Procedure:

Inject 20 µl volumes of blank, standard (6 injections)and sample (in single) in to the chromatograph.record the chromatogram and measure the peak areas of the sample and the standard solution.

For Vildagliptin

Calculate the mg Vildagliptin in tablets from the following expression

AT	WS	10	900	P	407.32	100
AS	100	100	1	100	523.32	LC

Where,

AT = Area of Vildagliptin in sample preparation

AS = Area of Vildagliptin in standard preparation

WS = weight of Vildagliptin working standard in mg

P =purity of Vildagliptin phosphate on unhydrous basis

407.32 and 523.32 are the molecular weight of Vildagliptin and vildagliptin phosphate.

LC =lable claim

For Metformin hydrochloride

Calculation; calculate the mg metformin hydrochloride in the tablet form the

following expression =

AT	WS	900	P	100
AS	100	100	LC	

Where,

AT = Area of Metformin hydrochloride in sample preparation

AT = Area of Metformin hydrochloride in standard preparation

WS = weight of Metformin hydrochloride working standard in mg

P = purity of Metformin hydrochloride working sample in mg

.

5,KINETICS STUDY

Kinetics of of Metformin hydrochloride release from the optimized batch was analysed by zero order, first order ,higuchi, peppas.

6. RESULTS AND DISCUSSION

The HPLC chromatogram and the linearity graph for vildagliptin and metformin hydrochloride are given in the figure:

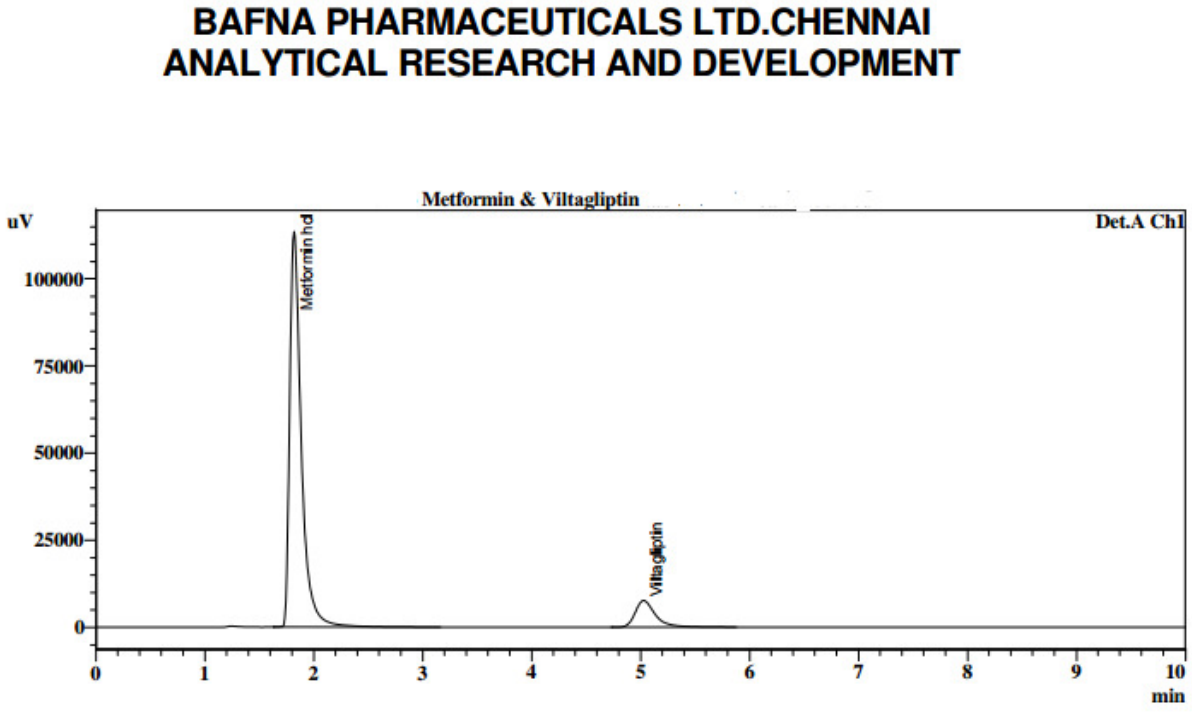
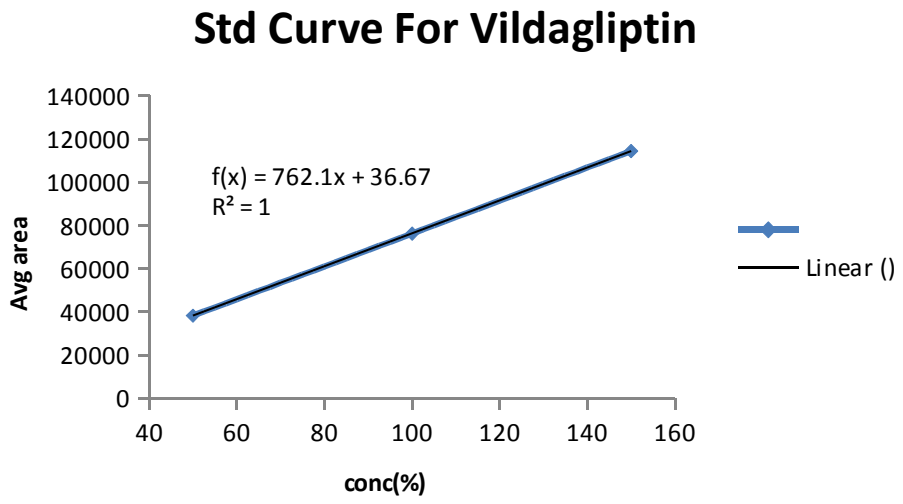


Fig no:7

Vildagliptin linearity curve

%	Avg area
50	38172
100	76186
150	114382

FIG ;8 STANDARD CURVE FOR VIDAGLIPTIN



Metformin hydrochlorid linearity curve

%	Avg area
50	483399
100	852002
150	1181596

FIG :9 STANDARD CURVE OF METFORMIN

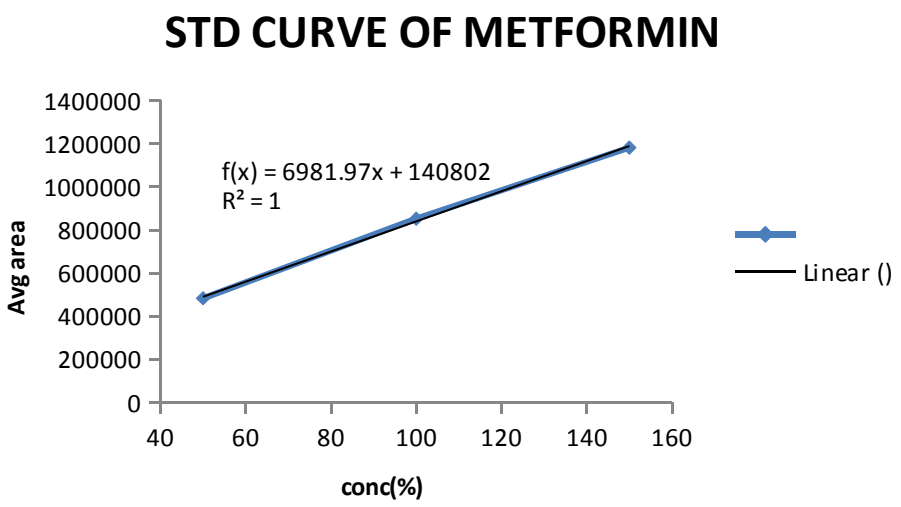


TABLE NO:7 PERCENTAGE OF DRUG RELEASED BY HPLC

Parts	Average area of chromatogram	% of drug released	Amount of drug released
Metformin SR	841010	97.27	486.35
Vildagliptin IR	97925	99.21	49.6

TABLE NO : 8 AVERAGE AREA OF CHROMATOGRAM FOR PERCENTAGE PURITY

Formulation	Average area of chromatogram for percentage purity	
	STD	SAMPLE
Metformin SR	858667	841010
Vildagliptin IR	98815	97925

TABLE NO :9 Evaluation of vildagliptin and metformim in granules are given in the table

S no	Preformulation character	vildagliptin	Metformin hcl			
			F1	F2	F3	F4
1	Angle of repose	22.49°	20 °	22°	21°	21.75°
2	Bulk density(g/cc)	0.880	0.843	0.782	0.781	0.751
3	Carr s index(%)	12.54	15.68	15.34	14.59	14.50
4	Hausner ratio	1.12	1.1055	1.1542	1.1459	1.1251

TABLE NO: 10 Tablets prepared were evaluated for weight and thickness which are given in the table

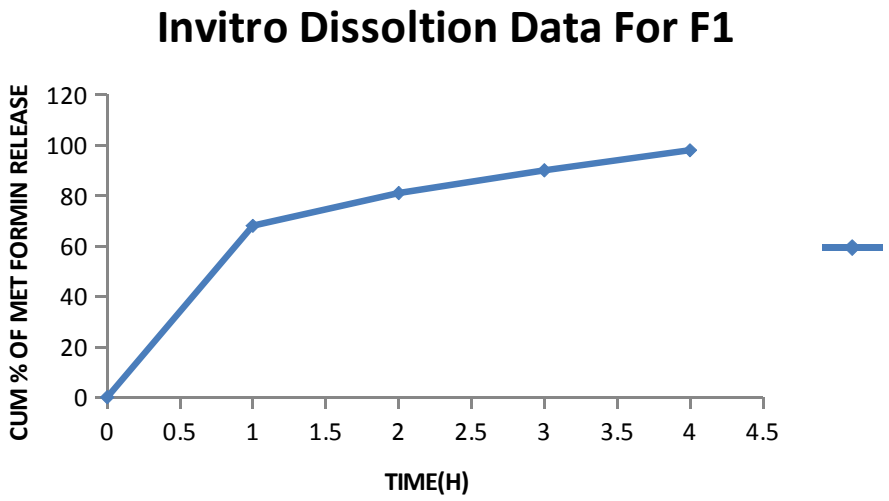
S NO	EVALUATION	FORMULATION			
		F1	**F2**	**F3**	**F4**
1	%Weight deviation	0.33%	0.60%	0.60%	0.58%
2	Average weight in (mg)	899	1014	970	940
3	Thickness(mm)	4.9	5.68	5.65	5.64

TABLE NO :11 DISSOLUTION

Time	**Percentage of drug release F1,F2,F3,F4**			
in	**F1**	**F2**	**F3**	**F4**

hours	cumulative amount of drug release	Cumulative % release	cumulative amount of drug release	Cumulative % release	cumulative amount of drug release	Cumulative % release	cumulative amount of drug release	Cumulative % release
1	340	68	92.21	18.44	95.44	19.08	154.09	30.82
2	406	81	121.4	24.29	135.302	27.06	204.5	40.9
3	450	90	179	35.8	180.22	36.04	246.82	49.36
4	490	98	251.05	50.21	298.85	59.77	331.36	66.27
5	……..	……..	305.9	61.18	311.25	65.25	368.15	73.63
6	…….	…….	335.7	67.14	356.6	71.32	399.55	79.9
8	……	…….	352.05	70.41	384.2	76.84	418.63	88.5
10	……..	. …….	381.75	76.35	401.10	80.22	440.45	97.27

FIG NO :10 INVITRO DISSOLUTION DATA FOR F1



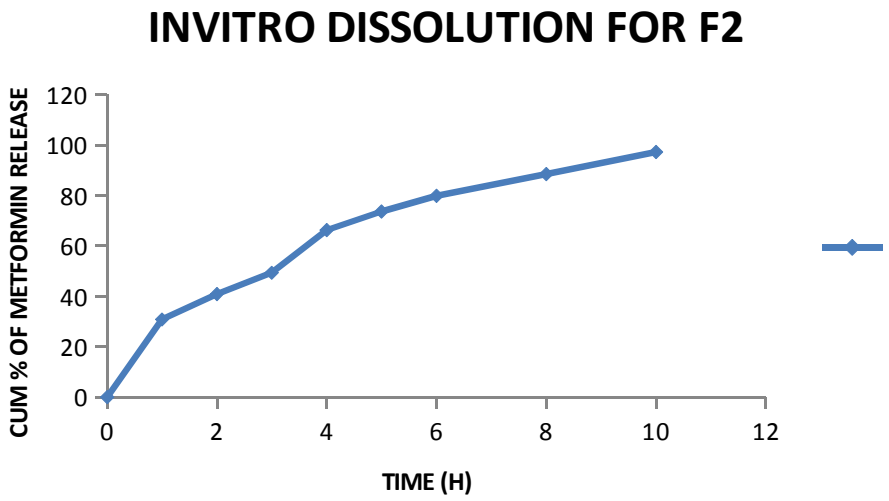
To get sustained release**,** HPMC K 100 mcr alone was used and tablet were prepared by direct compression. the was not sustained beyond 4 hours(table 11,fig:10) . Therefore the formula was modified with the inclusion of release retardant polymer at three stages,

1, Intra granular control release polymer HPMC K 100.

2, Extra granular control release polymer HPMC K 100.

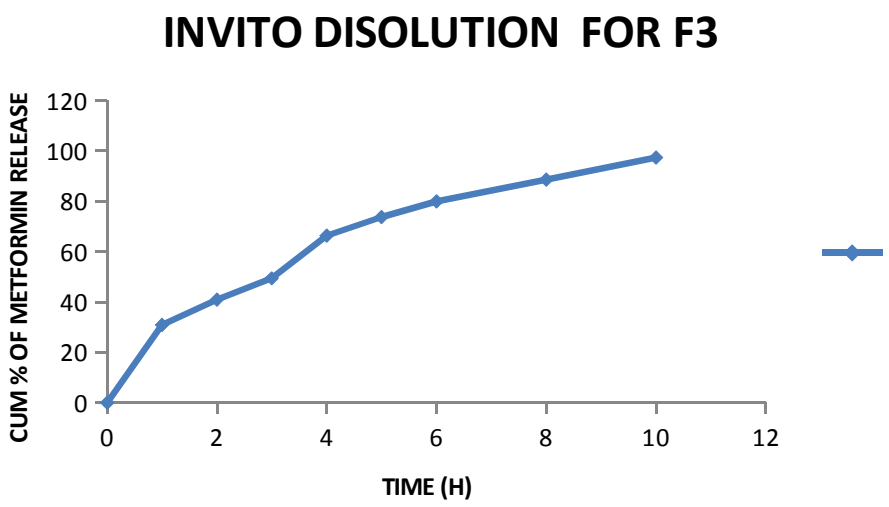
3,cross carmellose was included in the intra granular portion.

FIG NO: 11 INVITRO DISSOLUTION FOR F2



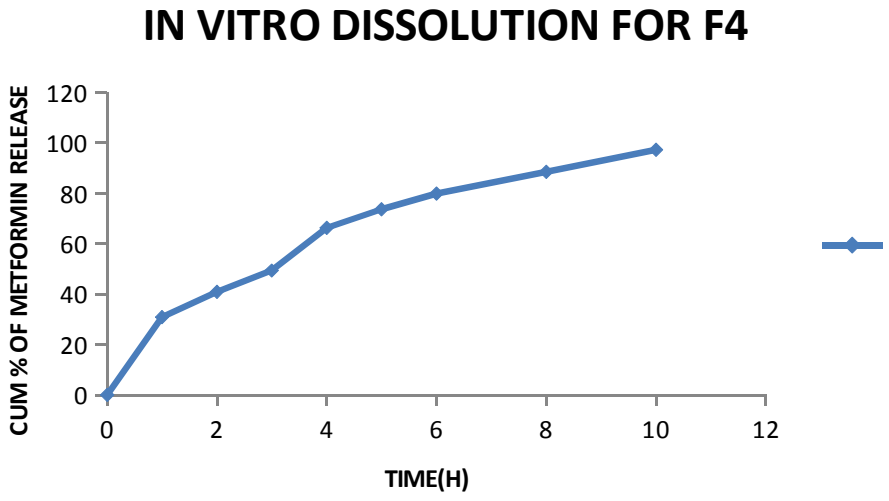
Even though F2 release showed prolonged release , the intial release not sufficient and does not match with the stipulated drug release.(table 11,fig 11) So F3 was prepared with the low level of intra and extra granular HPMC K100MCR and binding agent % was reduced from 8%-5%.

FIG NO: 12 INVITRO DISSOLUTION FOR F3



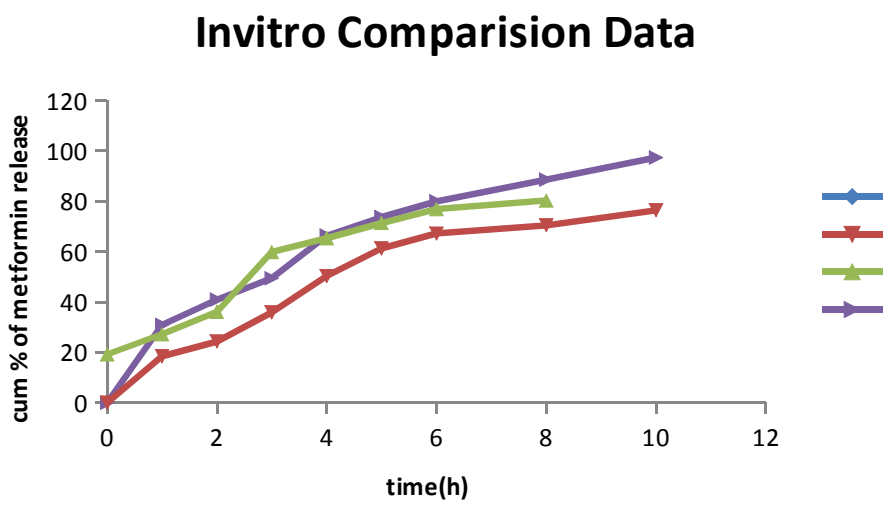
F3 the release was improved, but did not in the limit(table 11,fig.12) so intra granular HPMC K100MCR was excluded f4 was prepared.

FIG NO: 13 *IN VITRO* DISSOLUTION FOR F4



The release from F4 was found to be satisfactory.(table 11,fig no13). so release kinetic studies were perfumed

FIG NO: 14 INVITRO DISSOLUTION - COMPARISION



Kinetics of f4 was done the graphs are given in figures:

TABLE NO:12 DATA FOR KINETIC STUDIES

s.no	time	Route t	Log t	%cdr	Log %cdr	Cum % drug retained	Log Cum % drug retained
1	0	0	0	0	0		
2	1	1	0	30.82	1.4888	69.1	1.839
3	2	1.414	0.301	40.9	1.611	59.1	1.772
4	3	1.732	0.4771	49.36	1.693	50.6	1.704
5	4	2	0.6020	66.27	1.821	33.73	1.528
6	5	2.236	0.6989	73.63	1.8900	26.37	1.421
7	6	2.449	0.7781	79.9	1.9025	20.1	1.303
8	8	2.828	0.9030	88.5	1.946	11.5	1.190
9	10	3.162	1	97.27	1.9879	2.73	0.8129

FIG NO: 15 LOG CUM % OF METFORMIN RELEASE VS TIME

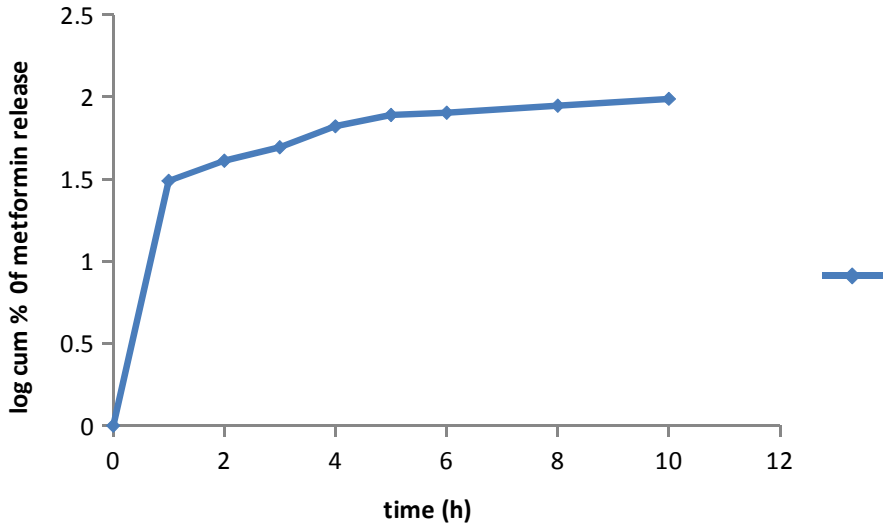


FIG NO: 16 ZERO ORDER GRAPH

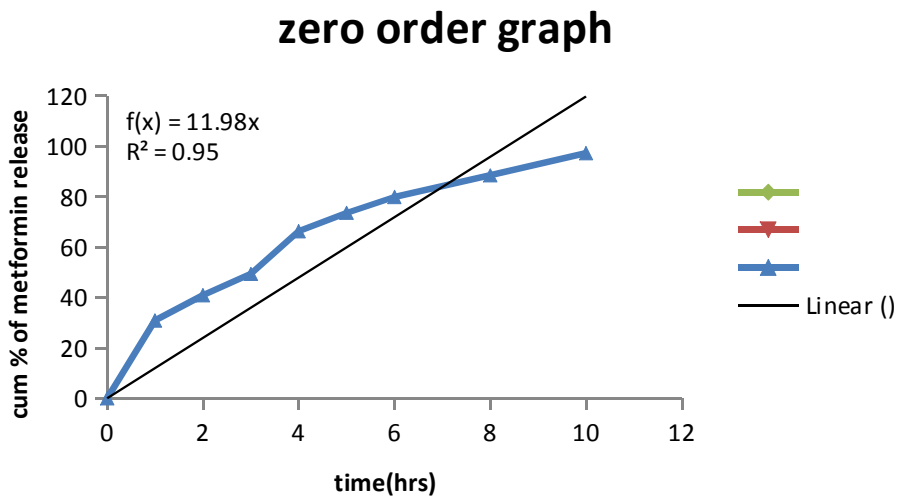


FIG NO: 17 FIRST ORDER GRAPH

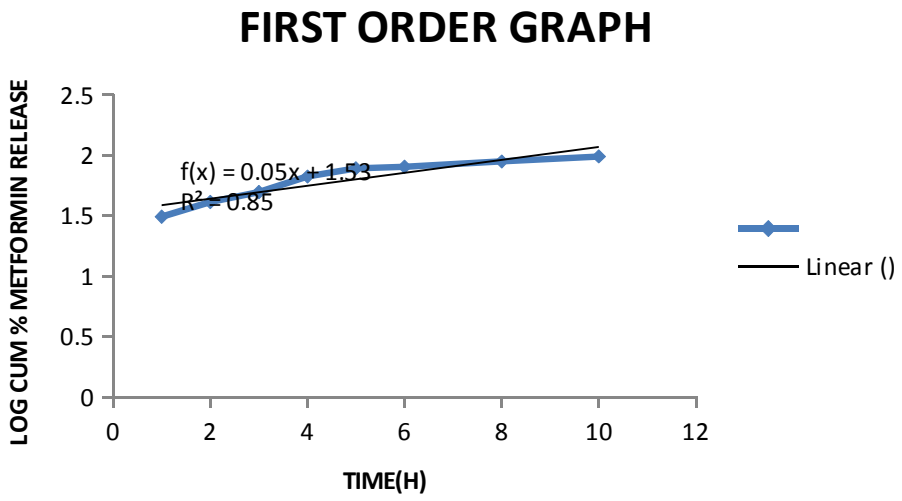


FIG NO:18 HIGUCHI PLOT

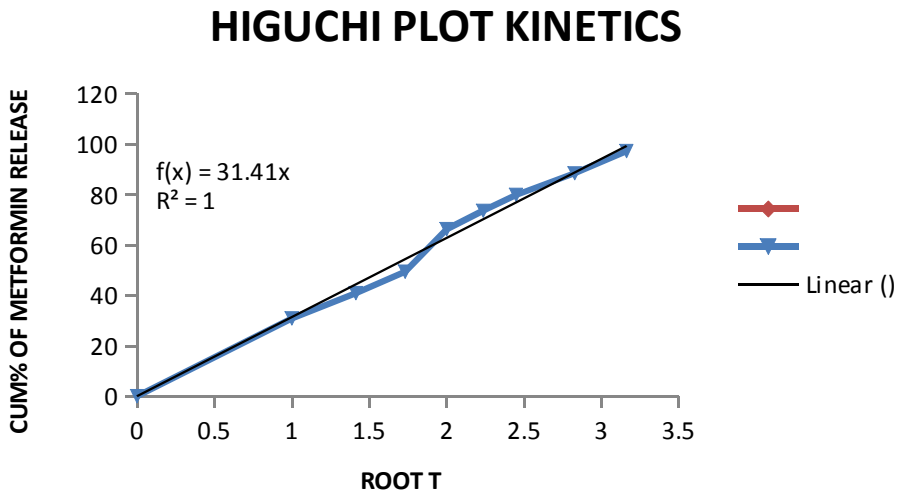


FIG :19 PEPPAS PLOT

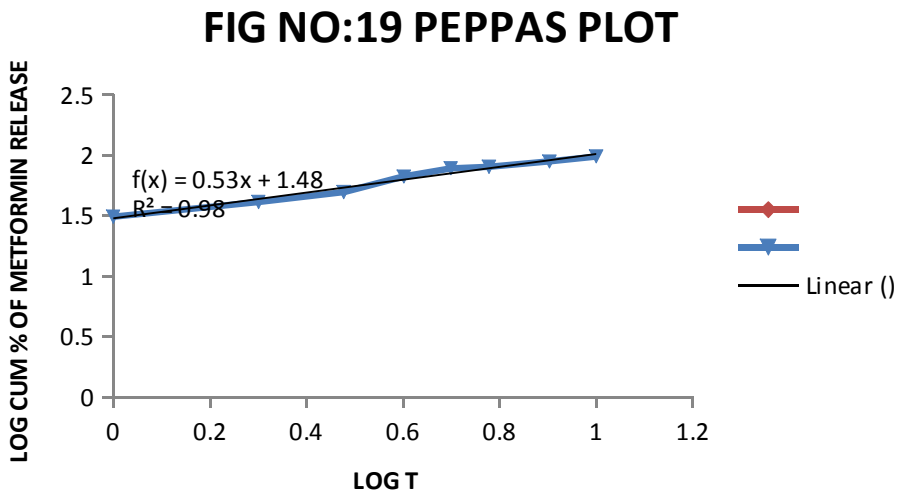


Table:13 RESULT OF KINETIC STUDIES FOR OPTIMIZED FORMULATION

S no	Formulation	Zero order R^2	First order R^2	Higuchi R^2	Koresmayer peppas R^2	Mechanism of drug release
1	F3	0.774	0.850	0.990	0.976	Matrix diffusion and drug release through swollen matrix

The release was found to follow matrix diffusion.

7. SUMMARY AND CONCLUSION

Development of oral controlled release dosage form for a given drug involves optimization of the dosage from characteristics within the inherent constraint of gastro intestinal (GI) Physiology.

Bi layer tablets have become popular in recent time containing three drugs in a single dosage from. In the present work Metformin Hydrochloride, Vildagcliption was formulated in single bi layer tablet for the treatment of diabetic disorders. Among the two Drugs Metformin Hydrochloride has been used for improving glucose utilisaton and Vildagcliption for better insulin levels.

The present investigation was undertaken to develop once novel daily bilayer tablet of metformin hydrochloride as a sustained release, vildagliptin as immediate release.

When the bilayer tablet containing sustained release part and immediate release part is administered, the immediate release part is used to achieve therapeutic level immediately and it act as a loading dose. The sustained part releases the drug for prolonged period and acts as the maintenance dose.

Vildagliptin was formulated with excipients for immediate release. Semi synthetic cellulose polymers have become very important for controlling the release. Polymer, hydroxyl propyl methyl cellulose (Methocel K -100 MCR) by varying proportions and crosslinked polymers were used to control the release of the drug Metformin HCl.

A detailed literature survey has been carried out and the clinical effectiveness at the drug chosen for diabetic disorders as well as the general research work done on control release form. this has been presented in literature survey chapter (Chapter 2).

In chapter-3 of the thesis the aim, objectives and plan of work are presented.

In chapter-4 of thesis the materials used and the source and methods adopted for preparing the controlled release bi layer tablet formulation and their physical characterization as per IP specification are given. HPLC was used for analytical estimation of both the drug candidates.

Four different formulations of SR part of Metformin Hydrochloride and one formulation of IR part of vildagliptin were prepared and details of the formula used for preparing bi-layer tablet

were discussed. The tablets were evaluated for their physical parameters like weight variation test, friability test, thickness test, content uniformity test. percentage drug release determination was studied. There are five formulations in the present study. There are three formulations in present study

All these parameters F1, F2 ,F3and F4 the weight variation, friability, thickness, disintegration tests was found to be within limits. so the invitro release of the three drugs from the bi layer was studied, These results along with physical characterization results are given in result, and discussion chapter. The dissolution test was carried out for all the 4 batches using in 3 replicates from each batch.

The dissolution of metformin hydrochloride was carried out in pH 6.8 phosphate buffer for the required time. If any batch released the drug in a pattern different from the specified limits, no further work was done on such batches and all were discussed in results and discussion chapter.

The formulation 4 was only formulation which complies with the stipulated standard prescribed. As it is the bi layer tablet containing sustained portion with metformin hydrochloride along with immediate release portion Vildagliptin release also found out by using 900 ml of 6.8 Phosphate buffer medium and Paddle type of apparatus with 50 rpm. The dissolution studies were carried out for 45 minutes. At the end of 45 minutes, 49.7 mg out of 50mg of Vildagliptin was found to be released, The results obtained were found to comply with the official standard and 99.4% of the drug was released.

The drug release kinetic studies were carried out and the graphs were plotted.

The release of Metformin Hydro Chloride was found to follow matrix diffusion as evidenced by the linear cumulative % of drug release vs log cumulative % of drug release. The present study resulted in a successful development of a formulation for once a day dosage form containing Metformin HCI SR in one layer and Vildagliptin IR in another layer

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